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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



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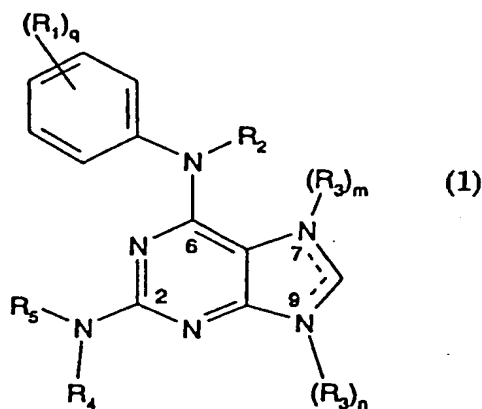
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 473/16, 473/00, 473/40		A1	(11) International Publication Number: WO 97/16452
			(43) International Publication Date: 9 May 1997 (09.05.97)
(21) International Application Number: PCT/EP96/04573 (22) International Filing Date: 22 October 1996 (22.10.96) (30) Priority Data: 3094/95 ✓ 1 November 1995 (01.11.95) CH 2213/96 ✓ 10 September 1996 (10.09.96) CH (71) Applicant (for all designated States except US): NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basle (CH). (72) Inventors; and (75) Inventors/Applicants (for US only): ZIMMERMANN, Jürg [CH/CH]; Ahornweg 622, CH-4323 Wallbach (CH). CAPRARO, Hans-Georg [CH/CH]; Habsburgerstrasse 60, CH-4310 Rheinfelden (CH). PETERLI, Patricia [CH/CH]; Metzgerstrasse 15, CH-4056 Basle (CH). FURET, Pascal [FR/FR]; 24, rue du Riegelsbourg, F-68800 Thann (FR). (74) Common Representative: NOVARTIS AG; Patent and Trade-mark Dept., Klybeckstrasse 141, CH-4002 Basle (CH).		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.	

(54) Title: PURINE DERIVATIVES AND PROCESSES FOR THEIR PREPARATION

(57) Abstract

2-Amino-6-anilino-purine derivatives of formula (1) in which the symbols are as defined in claim 1, are described. These compounds inhibit p34^{cdc2}/cyclin B^{cdc13} kinase and can be used for treatment of hyperproliferative diseases, for example tumour diseases.



MAY 1998

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 4-20624/A	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 96/04573	International filing date (day/month/year) 22/10/1996	(Earliest) Priority Date (day/month/year) 01/11/1995
Applicant CIBA-GEIGY AG et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ Certain claims were found unsearchable (see Box I).

2. ☐ Unity of invention is lacking (see Box II).

3. ☐ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing

☐ filed with the international application.

☐ furnished by the applicant separately from the international application,

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the title, ☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

Figure No. _____ ☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 13 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

National Application No

PCT/EP 96/04573

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D473/16 C07D473/00 C07D473/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 212 535 (BOEHRINGER MANNHEIM GMBH) 4 March 1987 see claims	1-16
A	WO,A,90 09178 (WHITBY RESEARCH INCORPORATED) 23 August 1990 see page 22 - page 29; claims	1-16

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

3 February 1997

Date of mailing of the international search report

12.02.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Luyten, H

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/04573

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-212535	04-03-87	DE-A- 3529497	26-02-87
		JP-B- 6092407	16-11-94
		JP-A- 62045588	27-02-87
		US-A- 4853386	01-08-89

WO-A-9009178	23-08-90	AU-B- 626983	13-08-92
		AU-A- 4941490	05-09-90
		EP-A- 0457773	27-11-91
		US-A- 5565566	15-10-96

PATENT COOPERATION TREATY

P. + T.M. Dept.	
17. April 1998	PCT4

1 MAY 1998

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

NOVARTIS AG
Patent and Trademark Dept.
Klybeckstrasse 141
CH-4002 Basle
SUISSE

Appl.
Specialist

Date of mailing (day/month/year) 14 April 1998 (14.04.98)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 4-20624/A	
International application No. PCT/EP96/04573	International filing date (day/month/year) 22 October 1996 (22.10.96)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address PETERLI, Patricia Metzerstrasse 15 CH-4056 Basle Switzerland	State of Nationality CH	State of Residence CH
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address IMBACH, Patricia Gstaltenrainweg 80 CH-4125 Riehen Switzerland	State of Nationality CH	State of Residence CH
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☒ the elected Offices concerned
☒ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Céline Faust Telephone No.: (41-22) 338.83.38
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INTERNATIONAL SEARCH REPORT

Inter. Natl Application No
PCT/EP 96/04573

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D473/16 C07D473/00 C07D473/40

01 MAY 1998

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 212 535 (BOEHRINGER MANNHEIM GMBH) 4 March 1987 see claims	1-16
A	WO,A,90 09178 (WHITBY RESEARCH INCORPORATED) 23 August 1990 see page 22 - page 29; claims	1-16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

3 February 1997

Date of mailing of the international search report

12.02.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Luyten, H

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 96/04573

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 13 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/04573

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-212535	04-03-87	DE-A- 3529497	26-02-87
		JP-B- 6092407	16-11-94
		JP-A- 62045588	27-02-87
		US-A- 4853386	01-08-89

WO-A-9009178	23-08-90	AU-B- 626983	13-08-92
		AU-A- 4941490	05-09-90
		EP-A- 0457773	27-11-91
		US-A- 5565566	15-10-96

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D	03 DEC 1997
WIPO	

09/05/827

Applicant's or agent's file reference 4-20624/A	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)
International application No. PCT/EP96/04573	International filing date (day/month/year) 22/10/1996	Priority date (day/month/year) 01/11/1995
International Patent Classification (IPC) or national classification and IPC C07D473/16		
Applicant NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 05/03/1997	Date of completion of this report 01.12.97
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Goss, I Telephone No. (+49-89) 2399-8292 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP96/04573

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-82 as originally filed

Claims, No.:

1-16 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP96/04573

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 13.

because:

☒ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

see Separate Sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP96/04573

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims..
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☐ all parts.
- ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-12,14-16
	No:	Claims	13

2. Citations and explanations

see Separate Sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP96/04573

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

2. Non-written disclosures (Rule 70.9)

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see Separate Sheet

Novelty

With regard to the requirements for novelty the essential structural difference between the subject-matter claimed and that of D1 = EP-A-0 212 535 and D2 = WO-A-90 09178 resides in the presence of the $(R_1)_q$ -anilino group at position 6 of all three classes of the compounds claimed (namely compounds of general formula I, II as well as V).

The subject-matter claimed thus appears to be novel.

Inventive step

The problem underlying the present application, as stated by the Applicant, is to provide compounds having particularly valuable activity in treating hyperproliferative diseases, such as tumours and psoriasis.

D1 describes structurally related compounds however acting as antiallergic agents. D2 also relates to structurally related compounds being adenosine receptor antagonist useful in a different pharmacological field.

The solution proposed by the Applicant resides in the provision of the present compounds being 2-amino-6-anilino-purine derivatives substituted by the relevant distinguishing group attached at the 6 position (see novelty analysis above).

Data are given on pp. 18 to 20 where the compounds are assessed for their in vitro as well as in vivo activity however without any precise reference to which compounds have been actually tested. In this respect the Applicant is reminded that in order to judge if the compounds tested are indeed representative for the broadly defined matter for which protection is sought, further evidence is kindly required (as to what the general statements on pp.18 and 19 "the compounds of the formula I ...have an IC_{50} of.." exactly referred to).

Thus an inventive step cannot at present been recognized.

Industrial Applicability

For the assessment of the present Claim 13 on the question whether it is industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP96/04573

industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Clarity

In claims 1 and 2 each of the terms "lower" or "optionally substituted" as well as the terms coming out from their combination should be specified in accordance with the description pp.1 to 7 (in order to clearly defined R_4 or R_5 , claim 2 should be introduced into claim 1).

R_4 means i.a. acyl having 1-30 C atoms. Since a C_1 acyl does not exist, the Applicant should remove this defect.